PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JL-23356-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. **PCT/KR2004/002770**	International filing date *(day/month/year)* **30 OCTOBER 2004 (30.10.2004)**	Priority date *(day/month/year)* 30 OCTOBER 2003 (30.10.2003)

International Patent Classification (IPC) or national classification and IPC

C07D 501/22(2006.01)i

Applicant

CJ CORPORATION et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
11 MARCH 2005 (11.03.2005)	13 JANUARY 2006 (13.01.2006)

Name and mailing address of the IPEA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
KIM, Hee Jin
Telephone No. 82-42-481-5412

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/002770

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☒ This report is based on translations from the original language into the following language English, which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☒ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this reort as "originally filed" and are not annexed to this report)*:

   ☒ the international application as originally filed/furnished

   ☐ the description:
   pages _____ as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the claims:
   pages _____ as originally filed/furnished
   pages* _____ as amended (together with any statment) under Article 19
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the drawings:
   pages _____ as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)* : _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)*: _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/002770

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-16	YES
	Claims		NO
Inventive step (IS)	Claims	1-16	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1 : WO 02/68428 A1

D2 : US 4708825

D3 : US 4463179

D4 : US 4223134

D5 : WO 02/83692 A1

D6 : US 5171854

D1 discloses a preparation method of cephalosporin which comprises reacting a cephem compound with a 4-hydroxyphenylglycine whose carboxylic group is activated by pivaloyl chloride or disuccinamidyl carbonate.

D2 discloses a method for producing cephalosporin antibiotics which involves reacting a 7-aminocephalosporin derivative with phenylglycyl chloride hydrochlorides obtained by reaction of N-substituted phenylglycines with thionyl chloride and the gaseous hydrochloride.

D3 discloses thiol esters of 4-hydroxyphenylglycine effective as acylating agents for amines of 7-aminocephalosporin derivative.

D4 discloses silyated and enamine protected 4-hydroxyphenylglycine sodium salt useful for the acylation of cephalosporin nuclei.

D5 discloses that 3-(Z)-propenyl cephem compound is selectively prepared by reacting a phosphoranylidene cephem compound with acetaldehyde in the presence of base in a solvent mixture essentially comprising diethyl ether.

D6 discloses a method of raising the Z- to E-isomer ratio in a 3-propenyl cephem compound by conducting Wittig reaction in the presence of lithium halide.

(Continued on Supplemental Sheet.)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

1.Novelty and Inventive Step

(1) Concerning claims 1-6

Claims 1-6 relate to a method of preparing cephalosporin antibiotics which comprises reacting a cephem compound of formula (3) with 4-hydroxyphenylglycine derivative of formula (2) in the presence of base.

None of the prior art uses the 4-hydroxyphenylglycine derivative of formula (2) for the acylation of cephem compound, which is not considered obvious to a person skilled in the art. Moreover, the process of the present invention has an advantage to be carried out in a one-pot reaction.

Therefore, claims 1-6 of the present invention are considered to meet the requirements of Articles 33(2) and 33(3) PCT.

(2) Concerning claims 7-14

Claims 7-14 relate to a 4-hydroxyphenylglycine derivative of formula (2) and the preparation method thereof.

None of the prior art discloses the triphenylphosphorane salt derivative of 4-hydroxyphenylglycine as an activated derivative of 4-hydroxyphenylglycine for acylation reaction, whose structure is not related with the derivative of 4-hydroxyphenylglycine disclosed in the prior art.

Therefore, claims 7-14 of the present invention are considered to meet the requirement of Article 33(2) and 33(3) PCT.

(3) Concerning claims 15-16

Claims 15-16 relate to a method of preparing 3-(Z)-propenyl cephem compound of formula (3a) comprising reacting phosphoranylidene cephem compound of formula (5) with acetaldehyde in the presence of base in a solvent mixture comprising water, isopropanol and methylene chloride in the ratio of 1 : 3~6 : 11~14.

None of the prior art suggests the solvent system for raising the Z- to E-isomer ratio in 3-propenyl cephem compound.

For the analysis of the inventive step, D5 is considered the closest prior art. D5 suggests a two-phase solvent system, and the organic phase thereof essentially comprising a diethyl ether for raising the Z-isomer content. Also, D5 describes that it is difficult to raise the Z-isomer content to above 83% when Wittig reaction is conducted using a conventional organic solvent such as methylene chloride.

From the disclosure of D5, the solvent system of the present invention is not obvious to a skilled person in the art.

Therefore, claims 15-16 of the present invention are considered to meet the requirement of Article 33(2)
and 33(3) PCT.

2. Industrial applicability

Claims 1-16 have industrial applicability.